
Dysregulated endocardial TGFbeta signaling and mesenchymal transformation result in heart outflow tract septation failure.

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Public Summary:

This study connected two different signaling pathways, controlled by the protein TGFb and by the active form of vitamin A, in formation of the outflow tract of the heart. The outflow tract refers to the ascending aorta and pulmonary trunk. A previous study of ours had shown that the organization of the outflow tract was compromised when vitamin A signaling was altered, and explained this by alteration of TGFb. Here, we used this experimental model to identify the specific tissues that make (myocardium) and respond to (endocardium) TGFb.

Scientific Abstract:

Heart outflow tract septation in mouse embryos carrying mutations in retinoic acid receptor genes fails with complete penetrance. In this mutant background, ectopic TGFbeta signaling in the distal outflow tract is responsible for septation failure, but it was uncertain what tissue was responsive to ectopic TGFbeta and why this response interfered with septation. By combining RAR gene mutation with tissue-specific Cre drivers and a conditional type II TGFbeta receptor (Tgfb2) allele, we determined that ectopic activation of TGFbeta signaling in the endocardium is responsible for septation defects. Ectopic TGFbeta signaling results in ectopic mesenchymal transformation of the endocardium and thereby in improperly constituted distal OFT cushions. Our analysis highlights the interactions between myocardium, endocardium, and neural crest cells in outflow tract morphogenesis, and demonstrates the requirement for proper TGFbeta signaling in outflow tract cushion organization and septation.

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